REMARKS/ARGUMENTS

Claims 16-18 are pending in this application. Claims 16 and 17 stand rejected. Claim 16 has been amended and claim 18 has been withdrawn.

With respect to all claims, Applicants have not dedicated, disclaimed, or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Rejection under 35 U.S.C. §102(b)

The Examiner has rejected claims 16 and 17 under 35 U.S.C. §102(b) as allegedly being anticipated by Xu et al. U.S. Patent No. 6262245 (hereinafter "Xu"). Applicants disagree and respectfully submit that the Xu reference does not set forth each and every element of the rejected claims. As currently amended, claim 16 includes the following element:

> determining that the level of expression of a gene encoding the polypeptide shown as SEQ ID NO:123 in a test sample of prostate tissue cells obtained from said mammal is higher than the expression level in a control sample of known normal prostate tissue cells [Emphasis added]

Xu does not disclose this element. Example 2 in Xu describes the examination of J1-17 mRNA expression levels in both prostate tumor tissue and normal prostate tissue. However, it is clearly disclosed in Column 19, lines 46-50 that

> J1-17 and L1-12 appear to be specifically over-expressed in prostate, with both genes being expressed at high levels in prostate tumor and normal prostate but at low to undetectable levels in all the other tissues examined. [Emphasis added]

The methods of the present invention are directed to diagnosing the presence of a prostate tumor in a mammal by determining that the level of expression of the polypeptide shown as SEQ ID NO:123 in a test sample is higher than the expression level in a control sample. Example 2 of Xu does not provide data on such differential expression, instead it discloses that J1-17 is expressed at high levels in both tumor tissue and normal tissue. Therefore, Xu fails to disclose each and every element of the present invention. As Xu fails to disclose each and every element of the claims, it cannot anticipate the present invention under 35 U.S.C. §102(b). Applicants respectfully request the withdrawal of this rejection.

Rejection under 35 U.S.C. §§102(a) and 102(e)

The Examiner has rejected claims 16 and 17 under 35 U.S.C. §§102(a) and 102(e) as allegedly being anticipated by Gish et al. WO 02/30268 (hereinafter "Gish"). Applicants discuss below the dates that the reference is allegedly entitled to under §§102(a) and 102(e).

102(e)

Applicants submit that Gish is not appropriately applied by the Examiner under 35 U.S.C. §102(e). M.P.E.P 706.02(f)(1) I. (C) provides that where the potential 102(e) reference resulted from an international application, the international application must have designated the United States (see 706.02(f)(1) I. (C)(1)(b)). In the event the United States is not designated, the reference may be applied under 102(a) or 102(b) as of its publication date, or 102(e) as of any later U.S. filing date of an application that properly claimed the benefit of the international application (if applicable) (see 706.02(f)(1) I. (C)(2)). Gish did not designate the United States and has no later filed U.S. applications claiming benefit to it. As such it is only available as a 102(a) reference.

In addition, Applicants note that of the U.S. applications to which Gish claims priority to only one potentially qualifies under 102(e). U.S. Application No. 09/847,046 published on June 6, 2002 as U.S. Published Application No. 2002/0068036. However, a review of this published application reveals that it does not disclose SEQ ID NO:123 as recited in the pending claims. Therefore, Applicants submit that neither Gish nor any of its priority claimed U.S. applications qualify as a reference any earlier than its 102(a) date. Applicants respectfully request the withdrawal of this rejection.

102(a)

Applicants submit that Gish can only applied, if at all, under 102(a) as of its publication date of April 18, 2002. However, Applicants traverse the rejection and respectfully submit that Gish does not contain an enabling disclosure sufficient to support the rejection under 102(a).

A. Legal Standard for an Anticipatory Reference.

M.P.E.P. §2121.01 provides that an anticipatory reference must contain an "enabling disclosure" and further explains that a

reference contains an "enabling disclosure" if the public was in possession of the claimed invention before the date of invention. "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." *In re Donohue*, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985).

In a recent case, the Federal Circuit reaffirmed that "to be anticipating, a prior art reference must be enabling so that the claimed subject matter may be made or used by one skilled in the art." *Impax Labs., Inc. v. Aventis Pharms., Inc.*, 468 F.3d 1366, 1381 (Fed. Cir. 2006) (citing *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354 (Fed. Cir. 2003)). *See Bristol-Myers Squibb v. Ben Venue Laboratories, Inc.* 246 F.3d 1368, 1374, 58 USPQ2d 1508, 1512 (Fed. Cir. 2001) ("To anticipate the reference must also enable one of skill in the art to make and use the claimed invention."); *PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566, 37 USPQ2d 1618, 1624 (Fed. Cir. 1996) ("To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter.").

Enablement requires that "the prior art reference must teach one of ordinary skill in the art to make or carry out the claimed invention without undue experimentation." *Elan Pharms., Inc. v. Mayo Found.*, 346 F.3d 1051, 1057 (Fed. Cir. 2003) (*quoting Minnesota Mining and Manufacturing Co. v. Chemque, Inc.*, 303 F.3d 1294, 1301, 188 F.3d 1362,1369, 64 USPQ2d 1270, 1278 (Fed. Cir. 2002)). A finding of lack of enablement and a determination that undue experimentation is necessary requires an analysis of a variety of factors, including (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability in the art, (8) the breadth of the claims. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). All of the factors need not be reviewed when determining whether a disclosure is enabling. See, *Amylin, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the Wands factors "are illustrative, not mandatory. What is relevant depends on the facts.")

B. Application of the Legal Standard.

Gish is not an anticipatory reference because it does not enable that which it is asserted to anticipate. As currently amended, claim 1 includes the step of

> determining that the level of expression of a gene encoding the polypeptide shown as SEQ ID NO:123 in a test sample of prostate tissue cells obtained from said mammal is higher than the expression level in a control sample of known normal prostate tissue cells, wherein said higher level of expression is indicative of the presence of a prostate tumor in the mammal from which the test sample was obtained. [Emphasis added]

The present invention concerns a determination that a gene exhibits a higher level of expression in a test sample from a subject than in a control sample, which indicates the presence of a prostate tumor in the subject. Gish does not provide an enabling disclosure for the detection of an elevated level of gene expression as an indicator of prostate cancer.

As discussed above, the law is clear that it is not enough to name or describe the claimed subject matter, if it cannot be produced without undue experimentation. At best, Gish resorts to mere naming of the presently claimed subject matter that would require undue experimentation. Evidence of the lack of an enabling disclosure is provided in various sections throughout the reference, including those cited by the Examiner on page 2 of the February 20, 2007 Office Action. For example, the Examiner relies on Table 4 on page 139 of the reference in which a gene designated Unigene ID number Hs.98802 is listed as having an R1 value of 33.6. R1 is defined as the "Ratio of tumor to normal body tissue." It is stated in the text immediately above Table 4 that the ratio relates to differential gene expression of Hs.98802 in prostate tumor tissue and normal prostate tissue. However, this section is not enabling because differential expression does not provide guidance as to whether an increase or a decrease in gene expression of Hs.98802 is indicative of a prostate cancer disorder.

In addition, the Examiner relies on the following additional sections of Gish

> the present invention provides a method of detecting a prostate cancer-associated transcript in a cell from a patient, the method comprising contacting a biological sample from the patient with a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-16. [Page 3 lines 7-10]

> [i]n another method detection of the mRNA is performed in situ. [Page 59, line 25]

> [i]n a preferred embodiment, *in situ* hybridization of labeled prostate cancer nucleic acid probes to tissue arrays is done. [Page 61, lines 11-12]

Again, these sections do not constitute an enabling disclosure because the disclosure is limited to the detection of a transcript. There is no information on whether the detection of an increase or a decrease in transcript level is needed to indicate the presence of a prostate cancer disorder.

The Examiner also cites Example 1 at pages 91-97, which concerns methods that might be used for detecting the afore-mentioned transcripts, including the steps of RNA purification, cDNA synthesis, and *in vitro* transcription. Once again, this is not an enabling disclosure because it does not provide guidance on whether an increase or a decrease in the level of transcript is indicative of a prostate cancer disorder.

Other sections of Gish further illustrate the absence of any enabling disclosure. For instance, the reference discloses a

> method of diagnosing a disorder associated with prostate cancer . . . [that] comprises determining the expression of a gene of Tables 1-16, in a first tissue type of a first individual, and comparing the distribution to the expression of the gene from a second normal tissue type from the first individual or a second unaffected individual. A <u>difference in the expression</u> indicates that the first individual has a disorder associated with prostate cancer. [Emphasis added] [page 7, lines 12-17]

This section is not an enabling disclosure because it fails to specify whether the disorder is characterized by an increase or a decrease in gene expression. Instead, it relies on a difference in gene expression. Furthermore, Gish defines "prostate cancer sequences" as sequences that might be <u>upregulated or downregulated</u> in prostate cancer (page 29, lines 10-14) and states that "Tables 1-16 provide unigene cluster identification numbers, exemplar accession numbers, or genomic nucleotide position numbers for the nucleotide sequence of genes that exhibit <u>increased or decreased expression</u> in prostate cancer samples" [Emphasis added] (page 9, lines 3-5). This too is not an enabling disclosure because it fails to specify whether it is the detection of <u>an increase or a decrease</u> in the expression of a gene from Tables 1-16 that indicates the presence of prostate cancer.

Clearly, the consistent lack of specificity regarding differential gene expression throughout Gish implies that an increase or a decrease in expression are equally indicative of the presence of prostate cancer according to the methods taught by the reference. Gish resorts to the mere recitation of an enormous list of genes and methods of detecting transcripts. This is

meaningless information unless details are provided on what indicates the presence of prostate cancer. Gish fails to provide an enabling disclosure regarding the determining step recited in claim 1 because there is no information on whether an increase or a decrease in expression is indicative of a disorder associated with prostate cancer. As such, Gish provides no credible use for the gene expression information and is thus not an enabling disclosure.

A finding of lack of enablement and a determination that undue experimentation is necessary requires an analysis of a variety of factors. The most important factors that must be considered in this case include: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability in the art, (8) the breadth of the claims. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

1. The quantity of experimentation.

The quantity of experimentation is high. Tables 1-16 provide a huge number of unrelated genes. A person of ordinary skill in the art would have to both determine that the Hs.98802 gene would be an appropriate indicator for prostate cancer and then determine whether an increase or a decrease in the expression level of the gene in a test sample would indicate the presence of prostate cancer in the subject from which the sample was obtained.

2. The amount of direction or guidance presented.

As discussed above, Gish provides no direction or guidance regarding whether the Hs.98802 gene might be a suitable indicator for prostate cancer or whether an increase or a decrease in its expression would indicate the presence of a prostate cancer disorder.

3. Absence of working examples.

Gish is limited to prophetic examples and provides no relevant working examples.

4. Nature of the invention.

Gish states that its invention provides genes that are upregulated or downregulated in prostate cancer cells and methods of detecting a prostate cancer-associated transcript in a cell from a patient comprising contacting a patient sample with a polynucleotide that hybridizes to a sequence with at least 80% identity to a sequence as shown in Tables 1-16 (See Summary of the Invention, page 3).

5. State of the prior art.

As described in Gish, the prior art provides a multitude of genes that might be appropriate markers for detecting prostate cancer and methods that might be suitable for detecting expression of the genes.

6. Relative skill in the art.

It is well established that the level of skill in the art of cancer diagnostics is relatively high, and is typically represented by the knowledge of a Ph.D. scientist with several years of experience in the pertinent field.

7. Unpredictability in the art.

The unpredictability in the art is very high when all that is provided is a laundry list of genes and methods suitable for detecting gene expression. Without some indication of its importance and what expression profile is relevant, Gish's disclosure of Hs.98802 for prostate cancer diagnostic purposes is highly unpredictable.

Thus, in view of the above, since Gish does not describe which genes would be appropriate indicators for prostate cancer, does not describe whether an increase or decrease in gene expression is indicative of the prostate cancer, and does not provide any working examples; since the nature of the invention, state of the prior art, and relative skill in the art do not allow one of ordinary skill in the art to follow Gish; and since the unpredictability of biotechnological arts is high where a laundry list of genes is provided with no information on what genes are appropriate and whether increased or decreased expression is relevant, Applicants submit that the quantity of experimentation needed to practice the invention is undue and that Gish does not provide an enabling disclosure to one of ordinary skill in the art to make and use the present invention.

From the citations discussed above, and the totality of its disclosure, it is clear that Gish does not contain an enabling disclosure for a method as recited by currently amended claim 1 that comprises "determining that the level of expression of a gene encoding the polypeptide shown as SEQ ID NO:123 in a test sample of prostate tissue cells obtained from said mammal is higher than the expression level in a control sample of known normal prostate tissue cells, wherein said higher level of expression is indicative of the presence of a prostate tumor in the mammal from which the test sample was obtained." As Gish does not contain an enabling disclosure, it cannot support an anticipation rejection under 35 U.S.C. §102. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

CONCLUSION

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39766-0225 R1**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: July 20, 2007

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